PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
40564		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FI2003/000973	19.12.2003	20.12.2002
International Patent Classification (IPC) or national classification and IPC		
C07K 14/705, A61K 38/17, A61P 11/06, C12N 5/12, C12Q 1/68		
Applicant		
Geneos Oy et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☒ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.05.2004	06.04.2005
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Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2003/000973

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-88 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

pages _____ as originally filed/furnished

pages* _____ as amended (together with any statement) under Article 19

pages* 89-93 received by this Authority on 28-02-2005

pages* _____ received by this Authority on _____

☒ the drawings:

pages 1-42 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2003/000973

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The priority is considered valid. Documents WO03007187 A1, WO03025179 A1 and EP1365030 A1 are therefore not considered herein.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2003/000973

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-41	YES
	Claims		NO
Inventive step (IS)	Claims	1-41	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-41	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents are considered relevant:

D1) WO0148188 A1 & CAS RN 349590-17-6 & GenBank acc. no. BD095689
D2) WO0118206 A1
D3) WO0242458 A2
D4) WO0231145 A1 & CAS RN 413009-26-4
D5) WO0148015 A2
D6) WO0177137 A1 & CAS RN 369415-18-9
D7) WPI abstract AN 2001-610074 & JP2001245666 A & GenBank acc. no BD017045
D8) WO02063004 A2
D9) WO0196400 A2
D10) WO0218412 A1
D11) Polvi A. et al: "Physical map of an asthma susceptibility locus in 7p15-p14 and an association study of TCRG"
D12) EMBL Acc. No: BC031961, entry date 28-Jun-2002, & Strausberg et al: PNAS, December 24, 2002, vol. 99, no. 26 pages 16899-16903

Document D12 was not sited in the International Search Report, but are included herein due to its relevance to DNA encoding AAA1 polypeptides and AAA1 polypeptides. A corrected Search Report including these documents has been issued.

D1 shows a gene containing hydrophobic domains, seemingly 7 transmembrane domains characteristic to G protein-coupled receptors. The gene can be used in screening ligands, screening agonists or antagonists which are useful as drugs and diagnosing diseases in which the gene participates. The

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 7-9, 25, 29 and 36-37, referring to polymorphic sites shown in Tables 3 and 12-14 and haplotypes H2, H4 and H5, are not entirely clear and concise (see PCT Art 6). The reference sequence in the tables is SEQ ID NO: 1 and is not indicated which positions the listed polymorphisms have with reference to the other GPRA or AAA1 sequences. This makes it difficult to see which polymorphisms are covered by the claims, thus making the claims somewhat unclear.

Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☒ table(s) related to the sequence listing

   b. format of material

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on _____

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

sequence with CAS RN 349590-17-6 shows 100% identity with 370 of the 371 amino acids of SEQ ID NO 3 in the present application. See abstract and figure 11 and CAS RN 349590-17-6 and GenBank acc. no. BD095689.

D2 shows human G-protein coupled 7 transmembrane receptor and polynucleotides encoding the same. Antagonists and antibodies are contemplated and can be used in therapy. The gene is mentioned as an important target for therapeutic treatment of e.g. cancer. Probes, primers and vectors relating to the gene are mentioned. The polymorphism Gln344Arg shown in Table 7 of the present application is shown in sequence SEQ ID NO 2 of D2. See SEQ ID NOs: 1-2, p. 5 line 30-p. 6 line 19, p. 6 line 25-p. 7 line 1, p. 7 line 26-p. 8 line 7, p. 10 lines 19-30 and p. 14 lines 23-32.

D3 shows G-protein coupled receptors, antibodies to such receptors, methods of detecting such nucleic acids and receptors and methods of screening for modulators of the receptors. Identified nucleic acid sequences called TGR60 encode two proteins generated by alternative splicing of an mRNA. The amino acid sequence of TGR60 is 99% identical to SEQ ID NO:3 of the present application. It is stated that mutations in or dysregulation of such receptors expressed in certain cells can lead to e.g. autoimmune diseases and receptors expressed in the lung may be involved in disorders of pulmonary function. See p. 75-76 SEQ ID NOs: 7-10, [49], [58], [71], [217] and p. 83 claim 33.

D4 shows a G-protein coupled receptor protein, its DNA and methods where it can be used. See abstract, SEQ ID NO: 16 and CAS RN 413009-26-4 (which is 99% identical to SEQ ID NO: 3 of the present application and which shows the polymorphism Gln344Arg in Table 7 of the present application).

D5 shows a gene encoding a G protein-coupled receptor. Splice variants of the receptor are discussed. Cancer is mentioned as

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

a disease that can be treated by targeting the identified gene. Genetic screens identifying mutations in the gene is discussed. See SEQ ID NOs 25 and 12 (SEQ ID NO: 25 is 99% identical to SEQ ID NO: 3 of the present application and contains the polymorphism Asn107Ile shown in Table 7 of the present application), p. 10 lines 9-12, p. 14 lines 4-6, p. 16 lines 15-26, p. 19 lines 21-24, p. 62 lines 1-18 and p. 69 line 17-p. 71 line 24.

D6 shows a sequence (SEQ ID NO: 1962, CAS RN 369415-19-9) being 100% identical to SEQ ID NO: 15 of the present application.

D7 shows a sequence (SEQ ID NO: 19, GenBank acc. no.: BD017045) being 99% identical to SEQ ID NO: 2 of the present application. The variant form of the polymorphism T>C at nucleotide 1529 shown in Table 7 of the present application is included in the sequence. See also the abstract.

D8 shows a sequence (SEQ ID NO: 51) being 99% identical to SEQ ID NO: 2 of the present application. The variant form of the polymorphisms A>T and C>G at nucleotides 448 and 524 respectively, shown in Table 7 of the present application are included in the sequence. The sequence encodes a G-protein coupled receptor molecule. Variants such as molecules including SNPs as well as probes are covered. It is stated that the molecules appear to play a role in cell proliferative disorders. See also p. 28 lines 2-13, p. 14 lines 14-32, p. 77 lines 14-27 and p. 78 lines 6-12.

D9 shows a sequence encoding a G-protein coupled receptor molecule. Proliferative disorders are said to be associated to the molecules disclosed in the document. Therefore, genetic alterations in the gene can be used to determine if a subject is at risk for a disorder characterised by e.g. cellular proliferation. SEQ ID NO: 2 in D9 is 98% identical to SEQ ID NO: 3 of the present application and contains e.g. the variant form of the polymorphism Asn107Ile shown in Table 7 of the present application. See also SEQ ID NO:1, p. 69 lines 6-22

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

and p. 70 lines 1-21.

D10 shows the sequences SEQ ID NO: 53, CAS RN 402537-39-7 and SEQ ID NO:24, CAS RN 402537-11-5. 402537-39-7 is 1837 nucleotides long. Nucleotides 769-1732 of 402537-39-7 are 99% identical to nucleotides 510-1473 of SEQ ID NO: 12 of the present application and nucleotides 364-772 are 99% identical to nucleotides 1-409 of SEQ ID NO: 12 of the present application. The sequences encode a 305 and 43 amino acid long secreted polypeptide respectively.

D11 discloses an asthma susceptibility locus in 7p15-p14. A detailed physical map of the linkage region with structural and functional information of known genes is shown. It is stated that some other known or yet unidentified genes other than TCRG in the linkage region might show a stronger association to asthma. See p. 661 Figure 1 and p. 664.

D12 shows AAA1 protein mRNA. The sequence is 1546 nucleotides long and 99,739% identical to SEQ ID NO: 16 of the present application over 1533 nucleotides. See EMBL acc. no.: BC031961.

The present application relates to genes related to asthma and other IgE mediated diseases and methods and kits for detecting the risk of asthma and other IgE mediated disease.

The document D11 is regarded as being the closest prior art to the subject-matter of claims 1, 18, 24 and 34, and shows asthma susceptibility locus in 7p15-p14 (See p. 661 Figure 1 and p. 664).
The subject-matter of claims 1, 18, 24 and 34 therefore differs from this known susceptibility locus in that a 133kb haplotype block inside the region 7p15-14 and SNPs inside that block define haplotypes demonstrating association to asthma and other IgE mediated disease.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

The subject-matter of claims 1, 18, 24 and 34 is therefore novel (Article 33(2) PCT).

The problem to be solved by the present invention may therefore be regarded as providing methods for detecting the risk of asthma and other IgE mediated disease.
The solution to this problem proposed in claims 1, 18, 24 and 34 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons: The skilled person did not have a reasonable expectation of success using routine experimental methods and starting from D11, since the asthma-association was not linked to a long haplotype but to a short haplotype which was not predictable form prior art. Thereto, no single SNP had statistical power enough to act as a marker for disease susceptibility, and in order to define haplotypes family cohorts had to be studied. Claims 2-17, 19-23, 25-33 and 35-39 are dependent on claims 1, 18, 24 and 34 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

Of special interest is also document D3, which shows a G-protein coupled receptor identical to GPRA of the present application. It is stated that mutations in, or dysregulation of, such receptors expressed in certain cells can lead to e.g. autoimmune diseases. And that receptors expressed in the lung may be involved in disorders of pulmonary function. See p. 75-76 SEQ ID NOs: 7-10, [49], [58], [71], [217] and p. 83 claim 33. However, in the present application it is shown that GPRA is expressed in very different tissues. Thus, no conclusion based on prior art can be made about the effect of GPRA mutations in certain tissue.

Document D2 is considered to represent the closest prior art in relation to claim 40. The invention according to claim 40 differs from the method in D1 in that different SNPs are detected and that haplotypes instead of single SNPs are identified. It is stated claim 40 that SNPs selected from Tables 13 and 14 are detected and that the method is suitable for detecting haplotypes H1 to H7.
Due to these features, identification of haplotypes is

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

achieved by detection of SNPs and a diagnostic method for diseases in which AST1 SNPs participate is provided.
Consequently, with the background of D1, the problem is to provide a diagnostic method for diseases in which AST1 SNPs participate.
There is no indication in prior art that haplotype combinations are needed instead of single SNPs to diagnose diseases in which AST1 SNPs participate.
Consequently, the invention according to claims 40-41 is novel and is considered to involve an inventive step.
The same argumentation as above can be used starting with any one of documents D1 and D3-D10 and D12 in the place of D2.

Regarding claims 40-41: It seems that a disease-association has not been identified to all the haplotypes H1-H7. The disease-association provides the technical effect of the invention according to claim 40. The applicant states that it is shown in the application that haplotypes H2, H4 and H5 associate with asthma or asthma-related phenotypes such as high IgE.